The prenatal risk factors of schizophrenia-spectrum disorders: focusing on the impact of high birth weight on obstetric complications

Linda Rantanen, lääketieteen kandidaatti
Terveyden ja hyvinvoinnin laitos (THL)

Helsinki 16.2.2017
Tutkielma
linda.rantanen@helsinki.fi
Ohjaajat: professori Tiina Paunio ja tutkimusprofessori Jaana Suvisaari
HELSINGIN YLIOPISTO
Lääketieteellinen tiedekunta

THE UNIVERSITY OF HELSINKI - HELSINGIN YLIOPISTO

Tiedekunta/Osasto Fakultet/Sektion – Faculty	Laitos/Institution– Department
The Faculty of Medicine	Terveyden ja hyvinvoinnin laitos (THL)

Tekijä/Författare – Author

Linda Helene Rantanen

Työn nimi / Arbetets titel – Title

The prenatal risk factors of schizophrenia-spectrum disorders: focusing on the impact of high birth weight on obstetric complications

Oppiaine /Läroämne – Subject

Medicine

Työn laji/Arbetets art – Level	Aika/Datum – Month and year	Sivumäärä/ Sidoantal – Number of pages
Thesis	16.2.2017	43

Tiivistelmä/Referat – Abstract

A high birth weight (HBW) has quite recently been associated with an increased schizophrenia risk, but the link between a low birth weight (LBW) and schizophrenia is well-known. The purpose of this study was to analyze obstetric adversities – with the focus on the role of HBW - among 109 subjects chosen from the Finnish schizophrenia family study sample. The subjects had a schizophrenia-spectrum disorder or a genetically high risk of developing such a disorder.

HBW (≥4000 g, n=37), compared to normal birth weight, NBW (2600-3999, n=64), associated with post-term pregnancy (p=0.041) and higher maternal parity (p=0.017). Post-term pregnancy associated with labour complications (p=0.04) and a prolonged first stage of labour (p=0.003). A higher parity was associated with Caesarean section (p=0.009), prematurity (p=0.048) and fetal malpresentation (p=0.021). LBW (<2600 g, n=8), compared to NBW, associated with perinatal complications (p=0.017), twin pregnancy (p=0.002), prematurity (p=0.009) grand multiparity (p=0.019) and higher parity (p=0.002)

150 words.

Avainsanat – Nyckelord – Keywords

schizophrenia, obstetric complications, high birth weight, low birth weight

Säilytyspaikka – Förvaringställe – Where deposited

E-thesis

Muita tietoja – Övriga uppgifter – Additional information

1 Introduction 1
2 Literary analysis 2
2.1 Epidemiology 2
2.2 Symptoms 2
2.3 Premorbid features and the prodrome 3
2.4 Morbidity and mortality 4
2.5 Risk genes 4
2.6 Obstetric complications and schizophrenia 5
2.7 A low birth weight and schizophrenia 7
2.8 A high birth weight and schizophrenia 9
2.9 Possible mechanisms behind the association between a high birth weight and schizophrenia 10
2.10 The birth weight and symptoms in schizophrenia 11
2.11 Obstetric complications and genes 11
3 Goals of the study 13
4 The study material and the methods 14
5 Results 16
5.1 General results 16
5.2 Comparing the obstetric parameters in the high birth weight and normal birth weight groups 19
5.3 Parity and post-term pregnancy in the high birth weight and normal birth weight groups 23
5.4 Comparing the obstetric parameters in the low birth weight and normal birth weight groups 26
6 Discussion 27
6.1 The role of high birth weight, post-term pregnancy and grand multiparity 27
6.2 The role of low birth weight 32
6.3 The role of societal changes during the 1940s-1970s 32
7 Conclusions 33
Sources 35

1 Introduction

The term “schizophrenia” refers to a split mind. Hallucinations, delusions, deficits in motivation, neurocognitive and executive functioning are among the most important symptoms in schizophrenia. (1) Schizophrenia is a relatively rare disorder, with the global prevalence being 0.4-0.7 % (2). Its harmful impact on the individual’s quality of life and mortality is, however, significant. People with schizophrenia lead, on average, 12-15 years shorter lives than the general population, mostly due to an elevated risk of somatic diseases, but also because of the higher suicide rates among affected individuals. (1)

Due to the enormous harm caused by schizophrenia, it is important to be aware of the risk factors associated with developing the disorder, especially among individuals with a high genetic risk of developing the disease. Obstetric complications are among the most studied risk factors for schizophrenia and are the focus of this study.

In this study I analyzed the birth records of 109 Finnish individuals with a presumably genetically high risk of developing schizophrenia. The subjects were chosen from the Finnish schizophrenia family study sample, and the study sample include individuals born between 1940 and 1976 and diagnosed with a schizophrenia-spectrum disorder between 1969 and 1998 and their siblings. The study material consists of the birth records of these subjects and is discussed more in detail in chapter 4. It should, however, be noted that the most significant weakness in the study material is the significant amount of lacking data regarding many obstetric parameters.

My goal was to analyze the associations between various obstetric parameters and complications among these individuals. The focus was on analyzing the association between birth weight – especially high birth weight – and obstetric complications. The link between a high birth weight and schizophrenia is a relatively new finding, and a low birth weight has traditionally been the main focus. To my knowledge, six studies have so far replicated the association between a high birth weight and schizophrenia (3) (4) (5) (6) (7) (8). My primary goal was to analyze whether or not the newborns with a high birth weight had more adverse obstetric events compared to the normal weight group.

Adverse obstetric events were divided into three categories: pregnancy, labour and perinatal complications. The role of some complications was analyzed separately and not only as a part of complications in general. Birth weight was classified into three groups: low birth weight (<2600 g), normal birth weight (2600-3999 g) and high birth weight (≥4000 g). Besides birth weight, I also analyzed other parameters, such as the maternal parity. The results are discussed in detail in chapter 5.

2 Literary analysis

2.1 Epidemiology

In Finland, approximately 3.5 % of the population suffer from some psychotic disorder, and 1 % from schizophrenia specifically (9).

The course of the disorder is highly individual. Recovery – of various degrees – is the goal, with the patients being active and fairly independent. Still, it is important that the patients get help regarding areas of life in which total independence might be unrealistic, such as personal finance. The majority of affected individuals do recover from the psychotic periods with medical treatment, but the negative symptoms and the weakened cognitive and executive functions tend to prevail. (1) In Finland, 70 % of people with a non-affective psychotic disorder are on disability pension and only 7 % of people with schizophrenia are employed (9).

2.2 Symptoms

The disorder extensively affects the individual's cognition and the ability to function in everyday life. The symptoms of the disease can be divided into different dimensions. The positive symptoms implicate the psychotic symptoms, namely the delusions and hallucinations. (1) Most typical are auditory hallucinations and paranoid delusions, which often begin in early adulthood or late adolescence (10).

Negative symptoms include a lack of motivation, social withdrawal and a decrease in spontaneous speech. Neurocognitive problems are also an important part of the

disorder. These include impairments in memory, attention span and executive functions, among others. (1)

2.3 Premorbid features and the prodrome

The premorbid period refers to the time period before the onset of the psychotic symptoms. Many studies demonstrate the presence of premorbid problems in children who later develop schizophrenia. Early abnormalities and delays in motor development have consistently been associated with an increased risk of developing schizophrenia. Social, cognitive and behavioral impairments in childhood and adolescence are also associated with later schizophrenia. (11)

It should be noted that most premorbid problems tend to be subtle. Still, the findings are consistent with the dominating neurodevelopmental theory of schizophrenia. According to the theory problems in early development make up the building blocks for abnormal neural pathways, which lead to premorbid symptoms before the actual onset of the psychotic disease. Abnormal brain development starts as early as in the mother's womb. The already vulnerable brain then "takes hits" when the central nervous system matures during adolescence and early adulthood. Thus the onset of the psychotic symptoms would be the tip of the iceberg in the development of schizophrenia. (10) Some of the brain abnormalities seen in chronic patients seem to already exist at the onset of the disease, notably enlargement of the lateral and third ventricles, and a smaller-than-average brain size and hippocampus (12).

The prodromal phase is a term used for a set of symptoms before the actual psychosis. The prodrome may last from weeks to even years, and it typically begins in adolescence or early adulthood. It is characterized by depression and anxiety and abnormalities in cognition, perception, social functioning, motivation and sleep. Verbal and motor skills might further deteriorate, and the stress tolerance lowers. Social isolation or failure in school or at work is common before the onset of psychotic symptoms. (13)

2.4 Morbidity and mortality

The mortality rates of people with schizophrenia are higher than those of the general population – and this gap has all but narrowed in the last decades. People with schizophrenia die 12-15 years earlier than the general population. (1) A possible explanation could be that people with schizophrenia have been left behind in the developments made in the general population's health. Suicide deaths are 12 times higher than among the general population. (14) Still, the widening gap in mortality between people with schizophrenia and the general population is largely due to differences in somatic diseases (1).

The somatic comorbidities associated with schizophrenia are multifaceted in their origin. Probable explanations include unhealthy lifestyle choices, risky behaviors and a noncompliance regarding treatments and a tendency not to use health care services as much as the general population. It is also possible that both genes and prenatal adversities associated with schizophrenia are associated with other diseases, such as diabetes. The harmful side effects of second-generation antipsychotic medicines are known, as they are associated with weight gain and metabolic syndrome. Currently it is still unknown to what degree the second generation antipsychotic medicines affect the mortality among people with schizophrenia. (14)

2.5 Risk genes

Schizophrenia is heavily influenced by genetics – its hereditability is 64 % - 81 % (15). Concordance among monozygotic twins is almost 50 %. It should, however, be noted that gene-environment-interactions are an important part of genetics - a gene might not add to the risk of schizophrenia if there is not an environmental factor pushing it to do so. Gene variants associated with schizophrenia also overlap with genes associated with other neurodevelopmental disorders, such as autism. (10)

Genetic research is a rapidly developing field in schizophrenia research. So far, more than a hundred independent genetic associations have been found in genome-wide association studies (16), and rare variants which increase the disease risk substantially have also been identified (17, 18). It is noteworthy that many of the associated genes are related to the central nervous system, and in particular features thought to be disturbed

in schizophrenia. For instance, the DRD2 (D2 dopamine receptor) gene has been implicated – which is an important finding, since all antipsychotic medications are thought to work mainly through counteracting this receptor. The genes involved in calcium channels and glutamatergic neurotransmission and synapting plasticity have also been found to associate with schizophrenia. There also seems to be overlap between common and rare gene variants in schizophrenia. (16)

Immunologic genes have also been implicated. This is interesting considering the cumulating evidence that immunologic factors might have a role in the etiology of schizophrenia. Schizophrenia associations have been found both in genes playing a role in acquired immunity, (16) and in genes related to innate immunity (19).

2.6 Obstetric complications and schizophrenia

Adverse obstetric events have been associated with an increased risk of developing schizophrenia since the first half of the 20th century. Complications during pregnancy and delivery were both implicated in the large meta-analysis by Cannon et al in 2002, as were abnormalities in the growth of the fetus. Specific complications that were implicated were "*in order of effect size: diabetes in pregnancy, birth weight < 2000 g, emergency Caesarean section, congenital malformations, uterine atony, rhesus variables (comprising rhesus incompatibility, rhesus-negative mother, rhesus antibodies), asphyxia, bleeding in pregnancy, birth weight < 2500 g, and preeclampsia*". (20) Prenatal infections have also been implicated as a risk factor in many studies. Proposed mechanisms during the pregnancy include a possibly harmful effect of maternal immune activation, microglial hyperactivity and autoimmune factors. (21)

It is important to note that it has proven quite difficult to demonstrate associations between specific obstetric complications and schizophrenia. This is due to the fact that obstetric complications are not necessarily independent. Specific complications might also be so rare that there simply is not enough data. Another important point to emphasize is that the association between obstetric complications and schizophrenia seems to be quite modest for the most part; the odds ratios are usually below 2.0. The

fact that birth complications are quite common – 25-30 % when defined broadly – and schizophrenia relatively rare, illustrates this fact. (20)

Common denominators seem to exist regarding complications related to an elevated risk of developing schizophrenia. The most singled-out one is hypoxia or anoxia, and theoretically it could unite such diverse complications as bleeding and pre-eclampsia during the pregnancy, and complications of delivery such as asphyxia and emergency Caesarean section. The etiology might vary, but independent of the cause, the consequence is a lack of oxygen for the fetus, which might lead to abnormalities in the development of the central nervous system. (20) In a meta-analysis by John R. Geddes et al premature rupture of membranes (OR 3.1), prematurity (OR 2.4), and use of an incubator / resuscitation (OR 2.2) were the most "high risk" obstetric complications regarding the risk of later schizophrenia. All of these complications could be considered to be partly hypoxia-related. (22)

There is also evidence that hypoxia-related obstetric complications are particularly related to early-onset schizophrenia. In a study by Rosso and colleagues - with subjects derived from a 1955 Helsinki birth cohort - the likelihood of early-onset schizophrenia accumulated with increasing amounts of obstetric complications. Three or more hypoxic obstetric complications were related to a ten-fold risk of early-onset schizophrenia. The study did not find a significant association between later-onset schizophrenia and hypoxia-associated obstetric complications. (23)

Tyrone D Cannon et al, deriving their study material from the above-mentioned Helsinki birth cohort, demonstrated an association between hypoxic obstetric complications and neuroanatomical abnormalities – ie. a reduction in gray matter and an increase in cortical cerebrospinal fluid - among both schizophrenia patients and their siblings. The findings were even greater among subjects born prematurely and/or who were small for their gestational age when compared to subjects of a normal size and/or born full term. In fact, among the latter subjects the siblings of the patients did not show a reduction in gray matter compared to the control group. As for ventricular enlargement, an association with hypoxia-related obstetric complications was found only in patients. (24)

Among controls (unaffected subjects without a high genetic risk of developing schizophrenia) there was no association between fetal hypoxia and a reduction in gray matter or increase in sulcal cerebrospinal fluid, not even in prematures or those who were small for gestational age. The controls and the siblings of the patients had similar rates of hypoxia-associated obstetric complications. The results hint at an interaction between genes and obstetric complications, with the patients' brains being the most sensitive to hypoxic obstetric complications and the healthy controls being the least sensitive. (24)

It is important to note that the above mentioned studies and meta-analyses have mostly analyzed hypoxia as a hypoxia-related complication, not as an independent condition defined by blood sampling or otherwise methodically rigorous assessments of hypoxia in and of itself.

However, a large case-control study by Dalman et al defined asphyxia as Apgar < 7, with the scores being carefully examined by pediatricians. The study group found that asphyxia increased the risk of schizophrenia, with the OR being 2.7 and 4.5 when adjusting for possible confounding factors. Still – it should be noted that even the Apgar score is an imperfect tool to measure asphyxia. (25)

Besides hypoxia, maternal stress could play a role in the development of schizophrenia, through the effect of the mother's glucocorticoids on the hypothalamic–pituitary–adrenal axis of the fetus. Theoretically, the development of other relevant parts of the central nervous system could also be disrupted, such as the hippocampus. The stress might also contribute to an increased risk of obstetric complications. (26)

2.7 A low birth weight and schizophrenia

The association between schizophrenia and low birth weight (<2000 g or <2500 g) is well-known, although some inconsistencies exist in the literature, and the changing definition of a low birth weight has contributed to the problem. In the 2002 meta-analysis by Cannon et al the odds ratio between LBW (<2500 g) and schizophrenia was

1.7, and 3.9 if the definition was <2000 g. Most obstetric adversities impact the growth of the fetus, and it has been theorized that a low birth-weight is largely a window to the possible complications in pregnancy. Adversities during fetal life might manifest as a low birth weight. Maternal behavioral factors may also contribute, since mothers with schizophrenia have an increased tendency for potentially harmful choices, such as smoking and unsatisfactory attendance at maternal health care centers. (20)

The Barker hypothesis (= the thrifty phenotype hypothesis) is also of some interest. According to the hypothesis undernourishment, a low birth weight and/or intrauterine growth retardation are associated with later coronary heart disease and markers present in metabolic syndrome, including high blood pressure, obesity, impaired glucose tolerance, diabetes type II and dyslipidemias. Proposed mechanisms are various physiological, hormonal and metabolic changes in the fetus. (27) During the Dutch Hunger Winter, the offspring of mothers exposed to famine had an increased risk of developing schizophrenia (28).

Abel et al found in their large population-based cohort study of singleton live births in Sweden (1973-1984) and Denmark (1979-1986) that the increased schizophrenia risk did not only apply to the smallest (<2500 g) infants, but also to babies whose weight was categorized as normal, especially those in the lower range of normal. The risk of schizophrenia increased with an decreasing birth weight. In this study, high birth weight (>4500 g) was not associated with an elevated risk of developing schizophrenia. A low birth weight was also associated with other psychiatric disorders, such as affective and neurotic disorders and disorders related to substance abuse. (29)

Other studies have also found associations between a low birth weight and various psychiatric disorders besides schizophrenia: attention-deficit disorder (30), autism, especially for girls and when mental retardation or other developmental disorders were present (31), and affective disorders (29, 32).

2.8 A high birth weight and schizophrenia

The definition of macrosomia has varied from > 4000 g to >4200 g to >4500g. Macrosomia has increased in the past few decades as obesity and diabetes have gotten more common among mothers. Macrosomia is especially common in the Nordic countries; around 20 % of infants are ≥ 4000 g, and 4-5 % ≥ 4500 g. (33)

So far, six studies have found an association between high birth weight and schizophrenia. The first study pointing in this direction was a small study in 1997 by Hultman et al who found that a disproportionately high birth weight relative to the birth height associated with an increased schizophrenia risk (3). Later, in 2003, Gunnel and colleagues found, among males, an association between both a birth weight below 2500 g (HR 7.0) and above 4000 g (HR 3.4) and schizophrenia (4). A small study found that the OR for schizophrenia was 4.5 when the birth weight exceeded 4000 g (5).

In the Northern Finland 1966 Birth Cohort study (NFBC66) both a high birth weight (≥4500g, OR 2.4) and a low birth weight (<2500g, OR 2.5) increased the risk of schizophrenia (6). There was also an interaction between high birth weight and parental psychosis in the NFBC66: high birth weight was associated with increased risk if parental psychosis was also present (7).

A Finnish study by Wegelius et al in 2011 found that a high birth weight (> 4000 g) was linked to a 1.7-fold increase in the risk of developing schizophrenia, but there was no significant association between a high birth weight and primary psychotic disorder. The study did also not find a statistically significant association between a low birth weight and schizophrenia or primary psychotic disorder. Wegelius et al used the same study material – the Finnish schizophrenia family study sample - as I in my own study. (8)

2.9 Possible mechanisms behind the association between a high birth weight and schizophrenia

Since the focus on the association between high birth weight and schizophrenia is relatively new, possible mechanisms are speculative. As a high birth weight is associated with diabetes during the pregnancy (33), it has been proposed that an underlying maternal diabetes might be part of the explanation when it comes to link between a high birth weight and schizophrenia (8). In the earlier mentioned 2011 study by Wegelius et al, the association between maternal diabetes and schizophrenia in the offspring was significant, as was the association between a high birth weight and schizophrenia. In this study, a high birth weight did, however, not associate with maternal diabetes – thus making the case for a more complicated and multifaceted explanation model. (8)

Schizophrenia patients also have more first-degree relatives with insulin-dependent diabetes mellitus than control subjects, which could indicate an autoimmune process. Still, how an abnormal glucose metabolism and the development of the fetal brain interact is largely unknown. (20)

A high birth weight is associated with an increased risk of death in utero. Other risks include prolonged labour, fetal hypoxia, intensive care, shoulder dystocia, plexus injuries, operative/caesarian deliveries, hypoglycaemia and hyperbilirubinemia. (33)

A meta-analysis by Koyanagi et al analyzed macrosomia in 23 developing countries in Africa, Asia and Latin America. Risk factors for macrosomia were maternal diabetes, older maternal age, greater maternal height, BMI $\geq$ 35, higher maternal parity, male sex of the baby and post-term pregnancy. In the meta-analysis, Caesarean section was a considerable macrosomia-associated risk, partly due to labour dystocia and partly due to post-term delivery. (34)

2.10 The birth weight and symptoms in schizophrenia

Torniainen and colleagues found an association between low and high birth weight and poorer cognitive functioning in both persons with schizophrenia and their unaffected first-degree relatives, although more so in those with schizophrenia. The affected cognitive areas were working memory, visuospatial reasoning, processing speed and set-shifting. For a low birth weight, the research team suggested that besides prematurity, also metabolic and endocrinological changes and disruptions in the brain development - due to insufficient oxygen and nutrition – might play a role. For a high birth weight, adverse intrauterine conditions – perhaps especially related to maternal diabetes– and macrosomia-related labour complications were suggested as possible mechanisms. (35)

Low birth weight has been associated with slightly poorer cognitive functions among children in the general population, although the link is not clear. The effect of high birth weight is not a thoroughly explored topic. (36) In adults, a history of low birth weight and prematurity has also been associated with a lower than average educational level and possibly a slight weakening in cognitive functions (37). Freedman et al published a study in 2012 which found that a lower birth weight associated with certain cognitive impairments among schizophrenia-spectrum disorder patients, but not among unaffected controls. This is suggestive of a certain vulnerability among schizophrenia patients. (38)

In a study by Wegelius and colleagues, high and low birth weight associated with bizarre behavior, positive formal thought disorder, a flat affect and attentional deficits among schizophrenia-spectrum disorder patients. The deficits were the most severe in the low birth weight group. Positive symptoms (hallucinations and delusions) were not associated with birth weight. The study subjects were chosen from the Finnish schizophrenia family study sample, which I also used in my own study. (39)

2.11 Obstetric complications and genes

There are different models of viewing the gene-environment-interactions in the role of schizophrenia. The phenocopy model states that an individual can develop

schizophrenia if the environmental risk factors exceed a threshold, even if the individual in question does not have genetic risk factors. The fact that the prevalence of schizophrenia is much lower than that of hypoxic obstetric complications diminishes the believability of this explanation model. Even among those with a background of a serious hypoxic obstetric complication, only a minority develops schizophrenia. (26)

According to the gene-environment-covariation model schizophrenia-associated genes might increase the risk of obstetric complications, and the obstetric complications in and of themselves are pretty neutral regarding the schizophrenia risk (26). However, siblings of individuals with schizophrenia do not seem to have more hypoxia-related obstetric complications in their background than the general population (23). Gene-environment interaction and additive influences models state that the significance of environmental risk factors is dependent on genes – obstetric complications might be more hazardous for people with a genetic predisposition of developing schizophrenia (26). This is in line with the finding that schizophrenia patients and siblings of schizophrenia patients seem to be more sensitive to the effects of obstetric complications than healthy controls (24).

As for birth weight, Wegelius et al found probable evidence of interaction between variants of the NDE1 gene and a high birth weight (> 4000 g), with the consequence of the interaction being an increased risk of developing schizophrenia (40). The NDE1 gene has an important role in early brain development (41).

Jablensky and colleagues discovered in a population cohort study that mothers with schizophrenia were, in comparison to mothers without a psychiatric diagnosis, more likely to have lacking social support, a lower socio-economic status and a non-optimal age (younger than 20 or older than 34). The overall risk of obstetric complications was elevated if the mothers already had a diagnosis of schizophrenia during the pregnancy, but not if the psychotic disorder manifested after the pregnancy. The exceptions were placental abruption, a low birth weight and cardiovascular birth defects in the baby. These complications were significantly more common in mothers with schizophrenia compared to the general population regardless of whether the mother had schizophrenia at the time of pregnancy or had developed it later, which might hint at a genetic component for these particular complications. However, the study suggests that many

obstetric complications become more likely only when adverse behavioral patterns associated with mental disorders are present. (42)

Another interesting study was conducted by Suvisaari et al in 2012, and it monitored women with a schizophrenia-spectrum disorder and their offspring. Few significant differences were found in the obstetric complications in the high risk versus control mothers. The differences became more frequent if the mothers had developed the psychotic disorder before they gave birth. In this study, infections, hypertension during pregnancy, and placental abnormalities were associated with elevated risk of schizophrenia spectrum psychoses in offspring of mothers with schizophrenia spectrum disorders. (43)

It should, however, be noted that absence of proper evidence is not evidence of absence, and it is possible that all of these theoretical models have a grain of truth to them. It is possible that they apply to certain subgroups of affected individuals. It could also be that all genes and environmental factors might not follow the same rules or patterns of interaction.

3 Goals of the study

The study subjects were derived from a Finnish schizophrenia family study material that has previously been used to analyze the relationship between high birth weight and the risk of developing schizophrenia. In the study, an association between high birth weight and elevated schizophrenia risk has already been established. (8) The goal of this study was to complement what is already known about this Finnish schizophrenia family study sample by taking a closer look at the relationship between birth weight and obstetric complications.

The main focus was on analyzing the role of high birth weight (≥ 4000 g) in this group – how it relates to other obstetric parameters, such as pregnancy- or labour-related complications and perinatal health problems. The comparison group consisted of newborns within the normal birth weight range (2600-3999 g). The study also included eight subjects with a low birth weight (< 2600 g), but the focus was on comparing the high and normal birth weight groups. This study did not include a control group, ie a

group without a genetically high risk of developing schizophrenia. The goal was not to analyze whether or not obstetric complications – and high birth weight in particular – increase the risk of developing schizophrenia. Rather, the main purpose was to analyze the complications within this high risk study sample, and to observe whether or not birth weight significantly interacted with various obstetric events and parameters.

Obstetric complications were divided into three main categories: pregnancy, labour and perinatal complications. I did not separate risk factors – such as maternal hypertension – from actual obstetric complications, such as hypoxia. Thus, I classified risk factors as complications. In my text, I speak mainly about obstetric complications, even though in many cases "risk factor" would be a more appropriate term. This choice was made for the sake of simplicity. I also analyzed Caesarian section, the use of instruments during the delivery, placental abnormalities, twin pregnancies, fetal malpresentation, preterm labour (< 37 weeks) and post-term pregnancy (≥ 42 weeks), neonatal distress, the Apgar score at 1 minute after the delivery and grand multiparity (≥ 5 previous labours) as separate variables. Most complications were not analyzed as their own variables, but rather categorized in the three complication groups. This decision was based on the low prevalence of individual complications in the study material.

Some birth records also contained information about the height and head circumference of the infant, and the mother's weight as well as her number of previous pregnancies and labours. These parameters were also analyzed in their relation to the birth weight, and in the case of parity, its relation to obstetric complications.

4 The study material and the methods

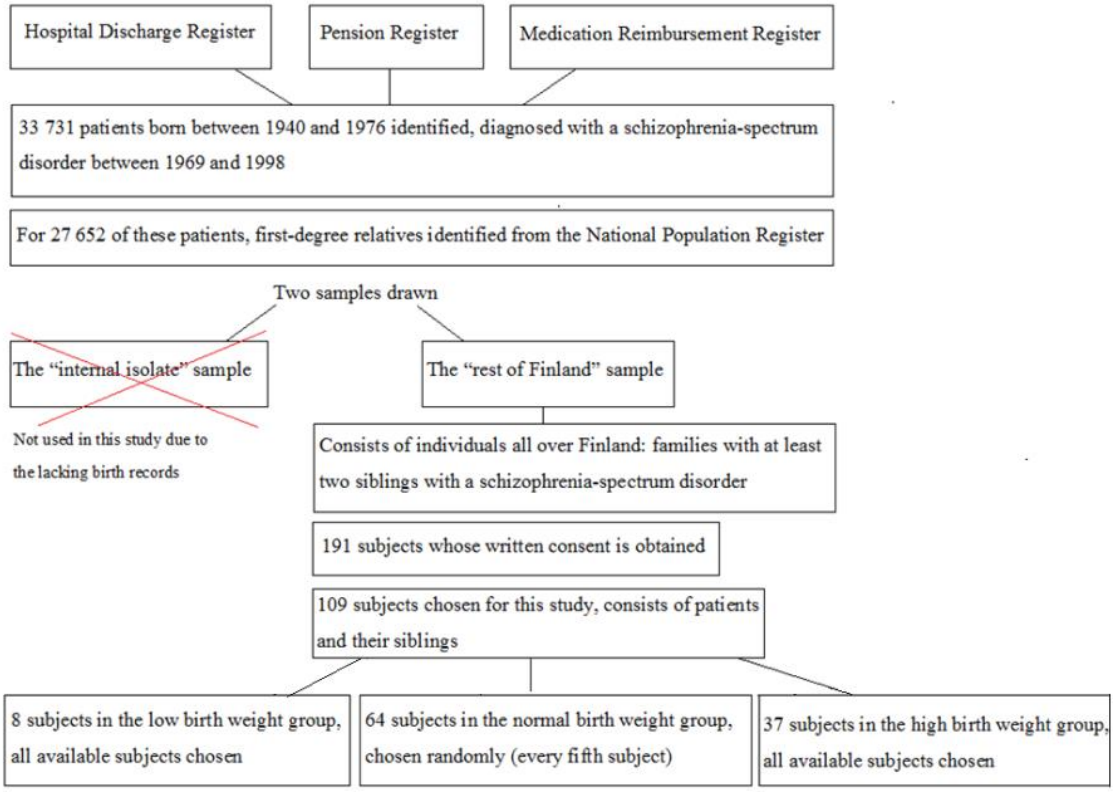
This study is based on a previously collected material, the Finnish schizophrenia family study sample. The study sample was originally identified from three national registers: the Finnish Hospital Discharge Register, the Pension Register and the Medication Reimbursement Register. 33 731 individuals diagnosed with a schizophrenia-spectrum disorder between 1969 and 1998 and born between 1940 and 1976 were identified from these registers. First-degree relatives of these individuals were identified from the National Population Register. The family information of 27 652 subjects was obtained.

Two samples were drawn in the original family study sample: an internal isolate and a "rest of Finland" sample. I only used the "rest of Finland" sample, as the birth records of the isolate sample were scarce and often lacking. In the "rest of Finland" sample, subjects were chosen from all over the country, and the sample consisted of families with at least two siblings with a schizophrenia—spectrum disorder, ie schizophrenia, schizoaffective disorder or schizophreniform disorder. (44)

For this study, all subjects with a high and low birth weight were chosen. A sample of infants with a normal birth weight was chosen randomly (every fifth participant). Thus, this study included 109 of the 191 subjects in the original "rest of Finland" sample. The subjects consist of individuals with a schizophrenia-spectrum disorder and their siblings. The written consent of these subjects has been previously obtained (44). The collection process of the study material is summed up in Picture 1 on page 16. For the majority of the subjects, the actual birth records were available, but for a small minority of the participants, only later records from child care centers were available.

I used SPSS version 24 to perform the analyses. For descriptive analysis of categorical variables, I used the Chi-square test. For analyzing potential associations, the Chi-square test or Fisher's Exact test (when the expected cell frequency was less than five) were used for categorical variables, and the Mann-Whitney test was used for continuous variables. I chose not to calculate the ORs or RRs due to the small size of the study sample and, in many cases, the missing data.

Picture 1. The study material and its collection process, summed up (44).



5 Results

5.1 General results

The study sample consisted of 109 subjects, of whom 62 (56.9 %) were male and 45 (41.3 %) female. In two cases the sex was unknown. The low birth weight group (< 2600 g) was called the LBW group, the normal birth weight group (2600-3999 g) was called the NBW group and the high birth weight group (≥ 4000 g) was called the HBW group. 8/109 (7.3 %) were in the LBW group, 64/109 (58.7 %) in the NBW group and 37/109 (33.9 %) in HBW group. Birth weight information was available for all subjects. Unfortunately, information about other obstetric parameters was scarcer. To see how much of the data was available regarding the different obstetric parameters in all of the weight groups, see table 1 below.

Table 1. The amount of available data regarding different obstetric parameters, in the different weight groups.

	LBW GROUP ***(<2600g)***	**NBW GROUP** ***(2600-3999g)***	**HBW GROUP** ***(≥4000g)***
Birth place (hospital / home)	4/8 (50.0 %)	56/64 (87.5 %)	26/37 (70.3 %)
Sex of infant	8/8 (100.0 %)	63/64 (98.4 %)	36/37 (97.3 %)
Height of infant	6/8 (75.0 %)	46/64 (71.9%)	24/37 (64.9 %)
Head circumference of infant	3/8 (37.5 %)	19/64 (29.7 %)	8/37 (21.6 %)
Mother's weight	0/8 (0.0 %)	16/64 (25.0 %)	5/37 (13.5 %)
Mother's height	3/8 (37.5 %)	20/64 (31.3 %)	8/37 (21.6 %)
Mother's number of previous pregnancies	2/8 (25.0 %)	43/64 (67.2 %)	18/37 (48.6 %)
Mother's number of previous labours	8/8 (100.0 %)	63/64 (98.4 %)	34/37 (91.9 %)
Duration of pregnancy	3/8 (37.5 %)	33/64 (51.6 %)	18/37 (48.6 %)
Pregnancy-related complications	4/8 (50.0 %)	51/64 (79.7 %)	25/37 (67.6 %)
Position of the infant during labour	3/8 (37.5 %)	43/64 (67.2 %)	24/37 (64.9 %)
Condition of the placenta	2/8 (25.0 %)	22/64 (34.4 %)	10/37 (27.0 %)
Duration of the first stage of labour	0/8 (0.0 %)	18/64 (28.1 %)	10/37 (27.0 %=
Duration of the second stage of labour	0/8 (0.0 %)	17/64 (26.6 %)	10/37 (27.0 %)
Caesarean section	8/8 (100.0 %)	61/64 (95.3 %)	35/37 (94.6 %)
Forceps/suction cup	6/8 (75.0 %)	55/64 (85.9 %)	29/37 (78.4 %)
Labour complications	6/8 (75.0 %)	53/64 (82.8 %)	27/37 (73.0 %)
Apgar score at 1 minute from the delivery	2/8 (25.0 %)	7/64 (10.9 %)	7/37 (18.9 %)
Signs of neonatal distress in the infant	7/8 (87.5 %)	60/64 (93.8 %)	33/37 (89.2 %)
Perinatal complications	5/8 (62.5 %)	28/64 (43.8 %)	15/37 (40.5 %)

Pregnancy-related complications found in the study were: pre-eclampsia (2 subjects), eclampsia (1 subject), maternal bleeding (2 subjects), albuminuria/proteinuria without pre-eclampsia (2 subjects), maternal infections (6 subjects), premature labour (12 subjects) and post-term pregnancy (9 subjects). Several of the mothers used iron supplements, but this was not classified as a complication as it is likely the supplements were taken routinely rather than as a treatment of anemia. Nausea, heartburn, headache, dizziness, overweightness, paleness, tiredness and swelling were not classified as

complications. One mother had an imminent miscarriage during the pregnancy, which was classified as a complication. It should be noted that one mother had slight bleeding in the beginning of the pregnancy, but this was not classified as a complication as this is a quite common (45).

I also included hypertension as a risk factor, and it was defined as the systolic blood pressure being, on average, ≥ 140 mmHg, or the diastolic blood pressure being, on average, ≥ 90 mmHg. If the mother had a systolic blood pressure of ≥ 150 mmHg or a diastolic blood pressure of ≥ 95 at least once during the pregnancy, this was also classified as high blood pressure. However, such measurements on the delivery day were not classified as hypertension. For the majority of the mothers, information about the blood pressure was unfortunately not available. 11 mothers were classified as being hypertensive. For two of these mothers, no actual data about their blood pressure was available, but the doctor or nurse had classified them as hypertensive. There was one mother who was hypertensive during a period of eclampsia, but I did not classify her as hypertensive as there was no information about her overall blood pressure during the pregnancy. There were two mothers who were advised to decrease the amount of salt in their food, but who did not fulfill the criteria of hypertension.

Complications during labour included Caesarean delivery (3 subjects), the use of a suction cup or forceps (8 subjects), green amniotic fluid (3 subjects), a calcified or disrupted placenta (8 subjects), abnormalities in fetal heart rate (1 subject), the umbilical cord being wrapped around the neck (5 subjects) fetal malpresentation, such as breech position (6 subjects). A prolonged labour was also classified as a complication, and the definition of a prolonged duration of the first stage in labour was >14 hours for mothers with previous labours and >20 hours for mothers without previous labours, and a prolonged second stage of labour was defined as >2 hours for nulliparous mothers and > 1 hour for multiparous mothers (46). Overall, 4 subjects had a prolonged first stage and 3 subjects a prolonged second stage.

Health issues in the newborns were hypoxia-associated problems such as breathing difficulties or being blue at birth (3 subjects), congenital abnormalities such as hip abnormalities or birth trauma (2 subjects) and neonatal distress defined as Apgar score at 1 minute < 8 or neonatal distress expressed in other terms in the birth records (1 subject). In the study sample, there was also a twin pair born during the thirty-first

week, and the birth record included the remark that they had been baptized as an emergency. I classified these twins as having a perinatal complication, even if the details of the birth were not disclosed in their birth records.

Due to the goals of the study, the focus was on the high birth infants. For the sake of clarity, I compared separately the HBW infants with the NBW infants, and then the LBW newborns with the NBW newborns. Thus, the NBW infants were the comparison group in both analyses.

5.2 Comparing the obstetric parameters in the high birth weight and normal birth weight groups

When comparing the NBW (2600-3999 g) and HBW (≥4000 g) groups, there was a significant (Fisher p = 0.025, χ^2 = 5.7) association between a HBW and pregnancy-related problems, with the occurrence being 60.0 % (15/25) in the HBW group, compared to the occurrence of 31.4 % (16/51) in the NBW group. Still, the significance disappeared when omitting post-term pregnancy from pregnancy complications (Fisher p = 0.43, χ^2 = 0.80). Post-term pregnancy made up 40.0 % of the pregnancy-related complications in the HBW group, and there was a statistically significant association between a high birth weight and being post-term as opposed to being born within the expected weeks (Fisher p = 0.041) .

High birth weight also associated with a taller height (p = 0.00, Mann-Whitney U 1003.0) and a larger head circumference (p = 0.025, Mann-Whitney U 118.0) in the newborn. The association between a high birth weight and being born at a hospital was somewhat below statistically significant (Fisher p = 0.070, χ^2 = 4.1)

There was no significant association between high birth weight and perinatal (Fisher p = 0.32) or labour complications (Fisher p = 0.13, χ^2 = 2.6). There was also no association between birth weight group and fetal malpresentation (Fisher p = 0.44), signs of neonatal distress in the infant (Fisher p = 0.36), prematurity of the infant (Fisher p = 0.71), a higher maternal weight (p = 0.66, Mann-Whitney U 34.0), the number of previous pregnancies (p = 0.46, Mann-Whitney U 434.0), twin pregnancy (Fisher p =

0.30), a calcified or disrupted placenta (Fisher p = 0.68), the duration of the first labour stage (p = 0.49, Mann-Whitney U 105.0), the duration of the second labour stage (p = 0.31, Mann-Whitney U 64.5), the Apgar score at 1 minutes from the delivery (p = 0.38, Mann-Whitney U 32.0), a Caesarean section (Fisher p = 0.53), the use of forceps or a suction cup (Fisher p = 0.66) or grand multiparity (Fisher p = 0.12, $\chi^2 = 2.7$). There was, however, a significant association between a high birth weight and a higher parity (p = 0.017, Mann-Whitney U 1386.0).

The associations between a high birth weight and various obstetric complications and events are listed in the table 2 on page 21. To see the mean and median values for the different obstetric parameters (such as birth height and maternal parity) in the different birth weight groups, see table 3 on page 22. The occurrences of various obstetric events and complications are listed in table 4 on page 23, also separately for each birth weight group.

Table 2. Associations between a high birth weight and obstetric complications and parameters, with infants with a normal birth weight as the comparison group.

	Test used in Spss 24	**Test Statistic**	**P value**
Pregnancy complications	χ^2	5.7	0.025
A higher number of previous pregnancies	Mann-Whitney U	434.0	0.46
A higher maternal parity	Mann-Whitney U	1386.0	0.017
Grand multiparity	χ^2	2.7	0.12
A twin pregnancy	Fisher's exact test		0.30
A higher maternal weight	Mann-Whitney U	34.0	0.66
A taller height of the infant	Mann-Whitney U	1003.0	0.00
A larger head circumference of the infant	Mann-Whitney U	118.0	0.025
Labour complications	χ^2	2.6	0.13
The use of forceps or a suction cup	Fisher's exact test		0.66
Caesarean section	Fisher's exact test		0.53
Abnormal fetal position	Fisher's exact test		0.44
Calcified or disrupted placenta	Fisher's exact test		0.68
Post-term pregnancy	Fisher's exact test		0.041
Prematurity	Fisher's exact test		0.71
A longer duration of the 1. stage of labour	Mann-Whitney U	105.0	0.49
A longer duration of the 2. stage of labour	Mann-Whitney U	64.5	0.31
Perinatal complications	Fisher's exact test		0.32
Being born at a hospital	χ^2	4.1	0.070
The Apgar score at 1 minute	Mann-Whitney U	32.0	0.38
Signs of neonatal distress	Fisher's exact test		0.36

Table 3. Comparing obstetric parameters in the three birth weight groups.

	LBW GROUP *(<2600 g)*	**NBW GROUP *(2600-3999g)***	**HBW GROUP *(≥4000 g)***
Mean head circumference	34.7 cm	35.3 cm	36.4 cm
Median head circumference	36.0 cm	34.5 cm	36.5 cm
Mean height at birth	43.9 cm	49.9 cm	53.0 cm
Median height at birth	43.0 cm	50.0 cm	53.0 cm
Mean number of previous pregnancies	11.0	4.1	4.9
Median number of previous pregnancies	11.0	4.0	4.0
Mean maternal parity	7.5	3.3	5.2
Median maternal parity	9.5	3.0	4.0
Mean duration of labour stage 1	No data	886 min	538 min
Mean duration of labour stage 2	No data	30 min	31 min
Median duration of labour stage 1	No data	320 min	393 min
Median duration of labour stage 2	No data	14 min	10.0 min
Mean duration of pregnancy	32.4 weeks	39.4 weeks	40.0 weeks
Median duration of pregnancy	31.4 weeks	39.6 weeks	40.1

Table 4. The occurrence of obstetric events and/or complications in the different birth weight groups.

	LBW GROUP (*<2600 g*)	**NBW GROUP (*2600-3999 g*)**	**HBW GROUP (*≥ 4000 g*)**
Pregnancy complication	¾ (75.0 %)	16/51 (31.4 %)	15/25 (60.0 %)
Labour complication	3/6 (50.0 %)	19/53 (35.8 %)	5/27 (18.5 %)
Perinatal complication	3/5 (60.0 %)	2/28 (7.1 %)	3/15 (20.0 %)
Disrupted or calcified placenta	0/2 (0.0 %)	5/22 (22.7 %)	3/10 (30.0 %)
Abnormal fetal position	1/3 (33.3 %)	4/43 (9.3 %)	4/24 (16.7 %)
Caesarean section	1/8 (12.5 %)	2/61 (3.3 %)	0/35 (0.0 %)
The use of forceps or suction cup	1/6 (16.7 %)	4/55 (7.3 %)	1/29 (3.4 %)
Post-term pregnancy	0/3 (0.0 %)	3/33 (9.1 %)	6/18 (33.3 %)
Prematurity	3/3 (100.0 %)	5/32 (15.6 %)	4/18 (22.2 %)
Signs of neonatal distress	0/7 (0.0 %)	0/60 (0.0 %)	1/33 (3.0 %)
Grand multiparity	6/8 (75.0 %)	19/63 (30.2 %)	16/34 (47.1 %)
Twin pregnancy	4/8 (50.0 %)	3/64 (4.7 %)	0/37 (0.0 %)
Born at hospital	4/4 (100.0 %)	35/56 (62.5 %)	22/26 (84.6 %)

5.3 Parity and post-term pregnancy in the high birth weight and normal birth weight groups

The risk of Caesarean section increased with higher maternal parity ($p = 0.009$, Mann-Whitney U 179.0) and with a higher amount of previous pregnancies of the mother ($p = 0.002$, Mann-Whitney U 116.5). The mother's mean parity was 11.0 in the cases where a Caesarean section was performed, and 3.9 among the mothers of subjects who were born vaginally. The mean number of previous pregnancies in cases which a Caesarean section was performed was 11.5, and 4.1 in cases where the baby was born vaginally.

Prematurity and a higher parity level also associated ($p = 0.048$, Mann-Whitney U 262.5), and the mean parity among mothers with a premature infant was 5.6, and among mothers whose baby was not premature the mean parity was 3.5. The association between a higher number of previous pregnancies and prematurity was approaching statistical significance ($p = 0.055$, Mann-Whitney U 236.0). The mean amount of

previous pregnancies among the mothers with a premature infant was 5.9. Among the mothers whose baby was not premature, the number was 3.8.

A higher parity was also associated with fetal malpresentation (p = 0.021, Mann-Whitney U 342.5), and the association between a higher number of previous pregnancies and an abnormal fetal position approached statistical significance (p = 0.056, Mann-Whitney U 234.0). The mean parity of mothers whose infants had an abnormal position at birth was 6.3 and among the mothers whose infants had a normal position at birth the number was 3.5. The mean number of previous pregnancies among mothers whose infants had an abnormal position was 5.9 and among mothers whose baby had a normal position at birth the number was 3.6.

A higher maternal parity also associated with the baby being born at a hospital rather than at home (p = 0.037, Mann-Whitney U 506.5). The mean parity among mothers who gave birth at a hospital was 4.5. Among those who gave birth at home, the mean parity was 2.6. Similarly, there was also a statistically significant association between a higher number of previous pregnancies and giving birth at a hospital (p = 0.021, Mann-Whitney U 219.5). Among the mothers who gave birth at a hospital, the mean number of previous pregnancies was 4.9 and among those who gave birth at home the number was 2.8.

Otherwise, the association between pregnancy-related complications and a higher parity was somewhat below statistically significant (p = 0.064, Mann-Whitney U 871.5). The same applied to the association between a higher parity and perinatal complications, with the p value being 0.065 (Mann-Whitney U 144.0). There was no association between a higher parity and labour complications (p = 0.92, Mann-Whitney U 682.0). There was no statistically significant association between the maternal parity and the condition of the placenta (p = 0.69, Mann-Whitney U 105.5), the use of forceps or a suction cup (p = 0.63, Mann-Whitney U 244,0), twin pregnancy (p = 0.51, Mann-Whitney U 175.0), signs of neonatal distress (p = 0.087, Mann-Whitney U 87.5), prolonged labour (p = 0.13, Mann-Whitney U 36.5), post-term pregnancy as opposed to delivery during the expected weeks (p = 0.12, Mann-Whitney U 199.5).

Grand multiparity (≥ 5 previous labours), when compared to normal parity, was associated with a higher maternal weight (p = 0.009, Mann-Whitney U 89.5), and the association to prematurity approached statistical significance (Fisher p = 0.055). Grand

multiparity also associated with being born at a hospital rather than at home (Fisher p = 0.013, χ^2 = 6.6). Grand multiparity was not associated with pregnancy-related complications (Fisher p = 0.22, χ^2 = 2.1), twin pregnancy (Fisher p = 1.00), labour complications (Fisher p = 0.80, χ^2 = 0.13), perinatal complications Fisher p = 0.17), a calcified or disrupted placenta (Fisher p = 1.00), Caesarean section (Fisher p = 0.13), the use of a suction cup or forceps (Fisher p = 1.00), the height of the infant (p = 0.86, Mann-Whitney U 526.0), the head circumference of the infant (p = 0.35, Mann-Whitney U 70.0), the maternal height (p = 0.76, Mann-Whitney U 83.0), fetal malpresentation at birth (Fisher p = 0.44), the Apgar score at 1 minute after the delivery (p = 1.00, Mann-Whitney U 25.0), signs of neonatal distress (Fisher p = 0.36), the duration of the first stage of the labour (p = 0.22, Mann-Whitney U 69.0), the duration of the second stage of the labour (p = 0.87, Mann-Whitney U 92.0), post-term pregnancy as opposed to delivery within the expected weeks (Fisher p = 0.11).

Post-term pregnancy significantly associated with labour complications (Fisher p = 0.040) when comparing to pregnancies classified as having a normal duration (37 weeks to 41 weeks and 6 days). Post-term pregnancy, as opposed to delivery within the expected weeks, also associated with a longer duration of the first stage of labour (p = 0.003, Mann-Whitney U 36.0). Naturally, post-term pregnancy associated with pregnancy-related complications (Fisher p = 0.00), as post-term pregnancy itself was categorized as a pregnancy-related complication. However, when omitting post-term pregnancy from pregnancy complications, the association disappeared (Fisher p = 0.31). Post-term pregnancy did not significantly associate with perinatal complications (Fisher p = 0.56).

Post-term pregnancy as opposed to delivery during the expected weeks did not associate with grand multiparity (Fisher p = 0.11), the use of forceps or a suction cup (Fisher p = 1.00), Caesarean section (Fisher p = 0.21), a calcified or disrupted placenta (Fisher p = 0.59), twin pregnancy (Fisher p = 1.00), the parity of the mother (p = 0.12, Mann-Whitney U 199.5), the number of previous pregnancies (p = 0.34, Mann-Whitney U 142.5), the maternal height (p = 0.082, Mann-Whitney U 33.0), the maternal weight (p = 0.73, Mann-Whitney U 16.0), the height of the infant (p = 0.086, Mann-Whitney U 187.0) or head circumference of the infant (p = 0.19, Mann-Whitney U 32.5), the duration of the second stage of labour (p = 0.15, Mann-Whitney U 8.5), fetal malpresentation at birth (Fisher p = 0.56), signs of neonatal distress (Fisher p = 1.00),

the Apgar score of the infant at 1 minute from the delivery (p = 0.19, Mann-Whitney U 16.0), being born at a hospital as opposed to at home (Fisher p = 0.69).

5.4 Comparing the obstetric parameters in normal birth weight and low birth weight groups

The study sample also included 8 infants in the low birth weight category (< 2600 g). I compared the LBW and NBW infants separately. The duration of the pregnancy was known in 3/8 cases, and in all of those cases the infants were premature – thus, they were classified as having a pregnancy-related complication. A twin pair in the LBW class was born at 31 weeks and 3 days, thus being classified as "very preterm". Both twins got an emergency christening. One subject was born with a Caesarean section. For more information about the obstetric parameters in the LBW group, see tables 3 and 4 on pages 22 and 23.

When comparing NBW and LBW infants, a low birth weight did not significantly associate with pregnancy (Fisher p = 0.11) or labour complications (Fisher p = 0.66) A low birth weight, however, significantly associated with perinatal complications (Fisher p = 0.017). Prematurity made up 3/5 of all pregnancy-related complications. One mother with a premature infant also suffered from pre-eclampsia and urinary stones.

The amount of twin pregnancies was also significant among the LBW infants compared to the NBW newborns (Fisher p = 0.002). The difference was quite big, as 50 % (4/8) of the LBW infants had a twin, whereas among the NBW infants only 4.7 % (3/64) had a twin. A low birth weight also associated with a smaller birth height (p = 0.00, Mann-Whitney U 273.5), prematurity (Fisher p = 0.009), grand multiparity (Fisher p = 0.019), a greater number of previous pregnancies of the mother (p = 0.012, Mann-Whitney U 3.0) and a higher maternal parity (p = 0.002, Mann-Whitney U 86.5).

A low birth weight did not associate with a smaller/bigger head circumference in the infant (p = 0.72, Mann-Whitney U 24.5), the maternal height (p = 0.31, Mann-Whitney U 41.5) a calcified or disrupted placenta (Fisher p = 1.00), Caesarean section (Fisher p =

0.31), the use of forceps or a suction cup (Fisher p = 0.42) or an abnormal position of the fetus at birth (Fisher p = 0.30). The Apgar score was known for only two LBW infants, and there was no association between the Apgar score and birth weight group (p =1.00, Mann-Whitney 7.0). There was no association between a low birth weight and being born at the hospital or at home (Fisher p = 0.29).

There was no data about the maternal weight or the duration of the labour in the LBW group.

6. Discussion

6.1 The role of high birth weight, post-term pregnancy and grand multiparity

The main goal of this study was to determine whether or not high birth weight associated with adverse obstetric events among schizophrenia-spectrum disorder patients and their siblings. The Finnish schizophrenia family study sample has been used in previous studies, and findings include an association between a high birth weight and schizophrenia-spectrum disorders (8) and, on the other hand, both low and high birth weight and behavioral and cognitive symptoms among schizophrenia-spectrum disorder patients (39). These findings are discussed more in detail in the literary analysis. It should, however, be mentioned that these studies have also included the Finnish isolate sample, which this study excluded due to lacking birth records.

In my study, I compared the infants in the high birth weight category to the infants with a normal birth weight. There was no significant association between a high birth weight and perinatal or labour complications. The association between high birth weight and pregnancy-related problems was significant (p = 0.025), but when post-term pregnancy was omitted from the pregnancy-related problems, the association became non-significant. (p = 0.43). In fact, post-term pregnancy (≥ 42 weeks) made up 40 % of the pregnancy-related problems in the high birth weight group. Post-term pregnancy was significantly more common among infants in the high birth weight group when compared to the infants in the normal birth weight group (p = 0.041). A third of the

macrosomic newborns were born post-term, while 9 % % of the normal birth weight babies were so. In this study, post-term pregnancy was associated with labour complications ($p = 0.040$) and a longer duration of the first stage of the labour ($p = 0.003$). Post-term pregnancy was not associated with perinatal complications ($p = 0.56$) or pregnancy-related complications ($p = 0.31$) when post-term pregnancy was omitted from being classified as a complication.

Previous studies have shown that the risk of complications - even perinatal death - is elevated in post-term deliveries. Several complications have been implicated, notably asphyxia, umbilical cord complications, bone fractures, peripheral nerve injuries, pneumonia and septicemia. Post-term delivery complications include cephalopelvic disproportion, dystocia and Caesarian section, for instance. Among post-term infants, the risk of both fetal and maternal complications is higher when the birth weight is either low (<2500 g) or high (≥4500 g) rather than normal (2500-4499 g). (47) My own study did not include any post-term infants in the low birth weight group.

A high birth weight is associated with aspiration and pneumonia among post-term infants; this might be due to more difficult deliveries. The risks post-term pregnancy entail are, however, not restricted only to the infants in the high or low birth weight categories. It is not known how much of the risks of post-term pregnancy are explained by prolonged pregnancy as such, and how much underlying factors – such as fetal health problems – could contribute to the occurrence of prolonged pregnancy. (47) It is also difficult to reliably analyze post-term pregnancy and high birth weight independently, since they are inherently interconnected. Macrosomia is approximately 4 times more common in pregnancies delivered at 41 weeks compared with 39 weeks and approximately 6 times more common when the baby is delivered at 42 weeks of gestation (48).

Dysmaturity syndrome is also more common among post-term than term babies. Characteristic features are exaggerated desquamation of the skin, long hair and nails, thinness, oligohydramnios and meconium passage. Dysmaturity is associated with certain risks, such as seizures, hypoglycemia and breathing difficulties in the infant. (49)

There is evidence that perinatal risks can be decreased if labour is induced before the pregnancy becomes post-term. Some of the risks are elevated already before 42 pregnancy weeks, and the official limit of 42 weeks is thus quite arbitrary. (49)

In my study, the duration of the pregnancy was based on the mother's last menstrual period. Ultrasonography is a more reliable method in predicting the delivery date, and a Finnish study found the difference in accuracy to be 1,7-3,5 days between these two methods. Using the last menstrual period as a predictor also seems to exaggerate the amount of post-term pregnancies. (50)

Another significant finding was the association between a higher maternal parity and a high birth weight when compared to the infants in the normal birth weight group ($p = 0.017$). Grand multiparity (≥ 5 previous deliveries) was, however, not significantly associated with high birth weight ($p = 0.12$). Previous studies have found a link between grand multiparity and high birth weight (51). Grand multiparity has also been associated with mental illness in the offspring (52), including schizophrenia (53).

In this study, there was no statistically significant association between grand multiparity and pregnancy, labour or perinatal complications ($p = 0.22$, $p = 0.80$ and $p = 0.17$) , but the association between a higher maternal parity and pregnancy-related ($p = 0.064$) and perinatal complications ($p = 0.065$) was somewhat below statistically significant. Grand multiparity was associated with a higher maternal weight ($p = 0.009$) and the association between grand multiparity and prematurity approached statistical significance ($p = 0.055$). The association between grand multiparity and a higher maternal weight might of course be due to maternal age – older women are more likely to have more labours in their history, and the weight might have accumulated with each pregnancy and as a natural part of aging. Previous studies have found a link between grand multiparity and maternal obesity (54).

The risk of a Caesarean section did increase with higher parity levels ($p = 0,009$), even if there was no statistically significant association between a Caesarean section and grand multiparity ($p = 0.13$) . The trend still pointed toward higher parity levels among mothers who underwent a Caesarean section. There was also a significant association between a higher maternal parity and prematurity ($p = 0.048$) and fetal malpresentation ($p = 0.021$). Grand multiparity was, however, not associated with an abnormal fetal position ($p = 0.44$).

Both grand multiparity ($p = 0.013$) and a higher parity ($p = 0.037$) were associated with the baby being born at a hospital rather than at home. This could be related to the fact that home births were very common during the period the subjects of this study were born. Thus, some prioritization may have taken place if there were increased risks of labour or perinatal complications. Similarly, the association between a high birth weight and being born at a hospital was somewhat below statistically significant ($p = 0.070$).

Grand multiparity has been associated with many obstetric complications: pregnancy-induced hypertension, medical illness of the mother, placenta praevia and prelabour rupture of fetal membranes, precipitate labour and failure to progress during labour and (overall) labour complications. Adverse perinatal outcomes have also been implicated, such as fetal distress, asphyxia, low Apgar scores, macrosomia and low birth weight, and an elevated perinatal mortality. (51) Fetal malpresentation has also been associated with grand multiparity in previous studies, and in my own study there was an association between a higher parity and malpresentation (55,56).

The evidence is somewhat contradicting regarding the risks of grand multiparity, and a systemic review found that while grand multiparity, when compared to normal parity, associates with macrosomia and some adverse obstetric events, it also associates with less frequent perinatal death. The systemic review also found that grand multiparity was associated with a decreased risk of induction, oxytocin use and the use of instruments during the delivery. The relationship between grand multiparity and Caesarean section is somewhat complex, as it seems to decrease among grand multiparous women but increase if the mother is "great grand multiparous", that is, if the amount of previous labours is ten or more. (54)

It is quite difficult to assess the meaning of these studies in regards to my own study, as the participants were born before the routine use of oxytocin, and when the likelihood of Caesarean section was undoubtedly smaller than in modern-day Finland, both due to the large amount of at-home births and the less specialized maternal wards and hospitals. There is reason to believe that risks associated with grand multiparity are significantly reduced in developed countries with good health care (57).

The role of grand multiparity is also quite unclear in modern-day Finland. The birth rate has decreased significantly compared to the birth rates during the first half of the 20th century, and the average Finnish woman gave birth to 1.7 children in 2014 (58). It has

been theorized that an "overt self-confidence" might be a problem among women who have given birth several times, as they are not as eager to book a time at the maternal health care center (54). However, in Finland the role of this is quite questionable. Finland has developed a very comprehensive maternal health care system (58). Considering all this, the clinical meaning of grand multiparity and its relation to possible obstetric complications – not to mention later mental illness in the offspring – is difficult to assess. It has been suggested that exposure to compromised parenting or to early socioeconomic adversity among the offspring born to grand multiparous mothers might also explain their increased risk of mental disorders (52).

A high maternal weight is a well-known risk factor for gestational diabetes, which, among other things, is a risk factor for a macrosomic baby (59). In my own study, information about maternal weight was, unfortunately, more often than not missing, and there was no significant relationship between the mother's and the infant's weight – which is perhaps more telling of the lacking data than a real lack of association. The participants in this study were born during a time when gestational diabetes was not routinely checked for, so any possible link between maternal diabetes and a high birth weight in the infant is merely speculative.

Still, there is some evidence suggesting that there has been a shift towards more diabetic/obese body proportions in macrosomic newborns, and that shoulder dystocia and Caesarean section have become more common among large infants compared to those born in the 1970s. Diabetes in the mother is a risk factor for shoulder dystocia. Thus, weight is not the only important parameter when determining the risks of macrosomia – also the body proportions and metabolic characteristics matter. (33) A high birth weight is, thus, not merely about weight, and it is quite possible that the heavy babies in this study represent a different body type than the heavier babies born in modern-day Finland.

6.2 The role of low birth weight

The infants with a low birth weight were compared to the infants in the normal birth weight category. The amount of participants in the low birth weight category was very small (8 participants). Those three subjects, whose mothers' last date of menstruation was known, were born prematurely. A low birth weight and prematurity associated significantly ($p = 0.009$). For the rest of the LBW infants, the duration of the pregnancy was not known, so it is impossible to know if their low birth weight was a case of prematurity or a case of being small for gestational age. Another significant finding was the association between a low birth weight and a twin pregnancy ($p = 0.002$) – in fact, half of the newborns in the LBW group were twins. Twin pregnancy itself is a risk for prematurity, low birth weight and growth retardation, Caesarean section, the use of forceps or a suction cup during the labour, pre-eclampsia and cholestasis of pregnancy (60).

Overall, a low birth weight did not associate with an increased risk of pregnancy ($p = 0.11$) or labour complications ($p = 0.66$). However, an association between a low birth weight and perinatal complications could be found ($p = 0.017$). Still, it is important to note that the well-being of the infant was known in only five of eight cases, and of these cases, three had a perinatal complication. In two of the cases, the newborn was classified as having a perinatal complication due to being very premature. The third subject developed respiratory distress syndrome soon after its birth.

A low birth weight also associated with grand multiparity ($p = 0.019$) and a higher parity ($p = 0.002$) in general. A link between a low birth weight and grand multiparity has been reported previously (51).

6.3 The role of societal changes during the 1940s-1970s

Most of the participants in this study were born during the 1940s-1970s when major changes in the maternal health care system were taking place. This is quite evidently reflected in the results; a significant amount of the subjects were born at home, and the occurrence of post-term pregnancies and grand multiparity was quite high.

The first maternal health care center in Finland was founded in 1926 in Helsinki, and in 1935 there were around twenty maternal health care centers in the country. In 1944, a national law demanded that every city, borough and rural municipality should have – by the time of 1949 – a physician-supervised maternal and child health care center. In 1944, there were only 259 maternal health care centers, but in 1960 the number was already 3244. Similarly, in 1944 % only 31 % of the mothers visited a maternal health care center, but in 1960 the attendance rate was 97 %.The number of visits also increased during this time. (61)

In the first half of the 20th century, there was a gradual transition from homebirths with a layperson as an assistant to homebirths in which a trained midwife was assisting. In 1940, the majority (70 %) of labours took place at home, but in 1960, 90 % of the deliveries occurred in hospitals. By 1970, the number approached 100 %. The quality of the maternal hospitals also developed, and a centralization process began, with the goal of having bigger and more developed units for deliveries. The centralization is still an on-going process in Finland. (62)

7 Conclusions

The societal developments during the 20th century are reflected in my study - both in some of the results and in the lacking data. Indeed, the major weakness in this study was the large amount of missing data, especially regarding perinatal complications. Birth records varied greatly in their amount and quality of information. In a few cases, no actual birth record was available, so the only available information was attained from later child health care center records, which had sparser information regarding the pregnancy and labour than the actual birth records.

The findings of my study were largely modest. No clear-cut conclusions about obstetric complications and high birth weight can be deduced based on this study. However, there were some suggestive findings pointing towards a certain trend of high birth weight being linked to maternal characteristics, such as higher parity and a longer gestational period. Post-term pregnancy, on the other hand, associated with an increased risk of

labour complications and a longer duration of the first stage of labour – which might put the infant at an increased risk of hypoxia. A higher parity was associated with an increased risk of Cesarean section, an abnormal fetal position and prematurity. The association between a higher parity and pregnancy and perinatal complications was somewhat below significant. To sum it up, the most important findings of this study are not directly related to high birth weight, but rather, to the characteristics that associate with high birth weight.

The "pro-obese" proportions of infants today are a challenge. These challenges are, luckily, somewhat counteracted by incremental steps towards a safer and better maternal care. Thus, the risks a high birth weight entail are not clear. On the one hand, the risks are easier to control in modern times, but on the other hand, the body proportions might be inherently unhealthier in the heavyset infants today than in the infants born during the decades from which this study material is collected.

The amount of babies with a low birth weight was so small that it would be unwise to make broad assertions about this group, especially since it is unclear how many of the infants were small due to prematurity or intrauterine growth retardation. The role of a low birth weight has undoubtedly changed since the subjects of this study were born, as increasingly premature neonates survive due to improved treatments.

The etiology and risk factors of schizophrenia have been extensively studied, but some of its multifaceted roots are undoubtedly still to be found. A high birth weight, and birth weight in general, is a quite crude parameter. In the future, we will hopefully get a more comprehensive view on the origins of schizophrenia, as information about genetics, obstetric complications and childhood development accumulates, and more interactions are detected.

Sources

(1) van Os J, Kapur S. Schizophrenia. Lancet. 2009 Aug 22;374(9690):635-45.

(2) Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. PLoS Med. 2005 May;2(5):e141.

(3) Hultman CM, Ohman A, Cnattingius S, Wieselgren IM, Lindström LH. Prenatal and neonatal risk factors for schizophrenia. Br J Psychiatry. 1997 Feb;170:128-33.

(4) Gunnell D, Rasmussen F, Fouskakis D, Tynelius P, Harrison G. Patterns of fetal and childhood growth and the development of psychosis in young males: a cohort study. Am J Epidemiol. 2003 Aug 15;158(4):291-300.

(5) Bersani G, Manuali G, Ramieri L, Taddei I, Bersani I, Conforti F, Cattaruzza MS, Osborn J, Pancheri P. The potential role of high or low birthweight as risk factor for adult schizophrenia. J Perinat Med. 2007;35(2):159-61.

(6) Moilanen K, Jokelainen J, Jones PB, Hartikainen AL, Järvelin MR, Isohanni M. Deviant intrauterine growth and risk of schizophrenia: a 34-year follow-up of the Northern Finland 1966 Birth Cohort. Schizophr Res. 2010 Dec;124(1-3):223-30.

(7) Keskinen E, Miettunen J, Koivumaa-Honkanen H, Mäki P, Isohanni M, Jääskeläinen E. Interaction between parental psychosis and risk factors during pregnancy and birth for schizophrenia - the Northern Finland 1966 Birth Cohort study. Schizophr Res. 2013 Apr;145(1-3):56-62.

(8) Wegelius A, Tuulio-Henriksson A, Pankakoski M, Haukka J, Lehto U, Paunio T, Lönnqvist J, Suvisaari J. An association between high birth weight and schizophrenia in a Finnish schizophrenia family study sample. Psychiatry Res. 2011 Dec 30;190(2-3):181-6.

(9) Perälä J. Epidemiology of Psychotic Disorders (dissertation). Helsinki, Finland; National Institute for Health and Welfare (THL); 2013. 130 p.

(10) Insel TR. Rethinking schizophrenia. Nature. 2010 Nov 11;468(7321):187-93.

(11) Schenkel LS, Silverstein SM. Dimensions of premorbid functioning in schizophrenia: a review of neuromotor, cognitive, social, and behavioral domains. Genet Soc Gen Psychol Monogr. 2004 Aug;130(3):241-70.

(12) Vita A, De Peri L, Silenzi C, Dieci M. Brain morphology in first-episode schizophrenia: a meta-analysis of quantitative magnetic resonance imaging studies. Schizophr Res. 2006 Feb 15;82(1):75-88.

(13) Larson MK, Walker EF, Compton MT. Early signs, diagnosis and therapeutics of the prodromal phase of schizophrenia and related psychotic disorders. Expert Rev Neurother. 2010 Aug;10(8):1347-59.

(14) Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry. 2007 Oct;64(10):1123-31.

(15) Lichtenstein P, Yip BH, Björk C, Pawitan Y, Cannon TD, Sullivan PF, Hultman CM. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. Lancet. 2009 Jan 17;373(9659):234-9.

(16) Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014 Jul 24;511(7510):421-7.

(17) Sing T, Kurki MI, Curtis D, Pucell SM, Crooks L, McRae J, Suvisaari J, Chheda H, Blackwood D, Breen G, Pietiläinen O, Gerety SS, Ayub M, Blyth M, Cole T, Collier D, Coomber EL, Craddock N, Daly MJ, Danesh J, DiForti M, Foster A, Freimer NB, Geschwind D, Johnstone M, Joss S, Kirov G, Körkkö J, Kuismin O, Holmans P, Hultman CM, Iyegne C, Lönnqvist J, Männikkö M, McCarroll SA, McGuffin P, McIntosh AM, McQuillin A, Moilanen JS, Moore C, Murray RM, Newbury-Ecob R, Ouwehand W, Paunio T, Prigmore E, Rees E, Roberts D, Sambrook J, Sklar P, St Clair D, Veijola J, Walters JT, Williams H; Swedish Schizophrenia Study.; INTERVAL Study.; DDD Study.; UK10 K Consortium., Sullivan PF, Hurles ME, O'Donovan MC, Palotie A, Owen MJ, Barrett JC. Rare loss-of-function variants in SETD1A are associated with schizophrenia and developmental disorders. Nat Neurosci. 2016 Apr;19(4):571-7.

(18) CNV and Schizophrenia Working Groups of the Psychiatric Genomics Consortium.; Psychosis Endophenotypes International Consortium.. Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects. Nat Genet. 2017 Jan;49(1):27-35.

(19) Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N, Tooley K,Presumey J, Baum M, Van Doren V, Genovese G, Rose SA, Handsaker RE; Schizophrenia Working Group of the Psychiatric Genomics Consortium., Daly MJ, Carroll MC, Stevens B, McCarroll SA. Schizophrenia risk from complex variation of complement component 4. Nature. 2016 Feb 11;530(7589):177-83.

(20) Cannon M, Jones PB, Murray RM. Obstetric complications and schizophrenia: historical and meta-analytic review. Am J Psychiatry. 2002 Jul;159(7):1080-92.

(21) Suvisaari J, Mantere O. Inflammation theories in psychotic disorders: a critical review. Infect Disord Drug Targets. 2013 Feb;13(1):59-70.

(22) Geddes JR, Verdoux H, Takei N, Lawrie SM, Bovet P, Eagles JM, Heun R, McCreadie RG, McNeil TF, O'Callaghan E, Stöber G, Willinger U, Murray RM. Schizophrenia and complications of pregnancy and labor: an individual patient data meta-analysis. Schizophr Bull. 1999;25(3):413-23.

(23) Rosso IM, Cannon TD, Huttunen T, Huttunen MO, Lönnqvist J, Gasperoni TL. Obstetric risk factors for early-onset schizophrenia in a Finnish birth cohort. Am J Psychiatry. 2000 May;157(5):801-7.

(24) Cannon TD, van Erp TG, Rosso IM, Huttunen M, Lönnqvist J, Pirkola T, Salonen O, Valanne L, Poutanen VP, Standertskjöld-Nordenstam CG. Fetal hypoxia and structural brain abnormalities in schizophrenic patients, their siblings, and controls. Arch Gen Psychiatry. 2002 Jan;59(1):35-41.

(25) Dalman C, Thomas HV, David AS, Gentz J, Lewis G, Allebeck P. Signs of asphyxia at birth and risk of schizophrenia. Population-based case-control study. Br J Psychiatry. 2001 Nov;179:403-8.

(26) Mittal VA, Ellman LM, Cannon TD. Gene-environment interaction and covariation in schizophrenia: the role of obstetric complications. Schizophr Bull. 2008 Nov;34(6):1083-94.

(27) de Boo HA, Harding JE. The developmental origins of adult disease (Barker) hypothesis. Aust N Z J Obstet Gynaecol. 2006 Feb;46(1):4-14.

(28) Susser E, Neugebauer R, Hoek HW, Brown AS, Lin S, Labovitz D, Gorman JM. Schizophrenia after prenatal famine. Further evidence. Arch Gen Psychiatry. 1996 Jan;53(1):25-31.

(29) Abel KM, Wicks S, Susser ES, Dalman C, Pedersen MG, Mortensen PB, Webb RT. Birth weight, schizophrenia, and adult mental disorder: is risk confined to the smallest babies? Arch Gen Psychiatry. 2010 Sep;67(9):923-30.

(30) Banerjee TD, Middleton F, Faraone SV. Environmental risk factors for attention-deficit hyperactivity disorder. Acta Paediatr. 2007 Sep;96(9):1269-74.

(31) Schendel D, Bhasin TK. Birth weight and gestational age characteristics of children with autism, including a comparison with other developmental disabilities. Pediatrics. 2008 Jun;121(6):1155-64.

(32) Wojcik W, Lee W, Colman I, Hardy R, Hotopf M. Foetal origins of depression? A systematic review and meta-analysis of low birth weight and later depression. Psychol Med. 2013 Jan;43(1):1-12.

(33) Henriksen T. The macrosomic fetus: a challenge in current obstetrics. Acta Obstet Gynecol Scand. 2008;87(2):134-45.

(34) Koyanagi A, Zhang J, Dagvadorj A, Hirayama F, Shibuya K, Souza JP, Gülmezoglu AM. Macrosomia in 23 developing countries: an analysis of a multicountry, facility-based, cross-sectional survey. Lancet. 2013 Feb 9;381(9865):476-83.

(35) Torniainen M, Wegelius A, Tuulio-Henriksson A, Lönnqvist J, Suvisaari J. Both low birthweight and high birthweight are associated with cognitive impairment in persons with schizophrenia and their first-degree relatives. Psychol Med. 2013 Nov;43(11):2361-7.

(36) Shenkin SD, Starr JM, Deary IJ. Birth weight and cognitive ability in childhood: a systematic review. Psychol Bull. 2004 Nov;130(6):989-1013.

(37) Tanskanen P, Valkama M, Haapea M, Barnes A, Ridler K, Miettunen J, Murray GK, Veijola JM, Jones PB, Taanila AM, Isohanni MK. Is prematurity associated with adult cognitive outcome and brain structure? Pediatr Neurol. 2011 Jan;44(1):12-20.

(38) Freedman D, Bao Y, Kremen WS, Vinogradov S, McKeague IW, Brown AS. Birth weight and neurocognition in schizophrenia spectrum disorders. Schizophr Bull. 2013 May;39(3):592-600.

(39) Wegelius A, Pankakoski M, Lehto U, Suokas J, Häkkinen L, Tuulio-Henriksson A, Lönnqvist J, Paunio T, Suvisaari J. An association between both low and high birth weight and increased disorganized and negative symptom severity in schizophrenia and other psychoses. Psychiatry Res. 2013 Jan 30;205(1-2):18-24.

(40) Wegelius A, Pankakoski M, Tomppo L, Lehto U, Lönnqvist J, Suvisaari J, Paunio T, Hennah W. An interaction between NDE1 and high birth weight increases schizophrenia susceptibility. Psychiatry Res. 2015 Dec 15;230(2):194-9.

(41) Bakircioglu M, Carvalho OP, Khurshid M, Cox JJ, Tuysuz B, Barak T, Yilmaz S, Caglayan O, Dincer A, Nicholas AK, Quarrell O, Springell K, Karbani G, Malik S, Gannon C, Sheridan E, Crosier M, Lisgo SN, Lindsay S, Bilguvar K, Gergely F, Gunel M, Woods CG. The essential role of centrosomal NDE1 in human cerebral cortex neurogenesis. Am J Hum Genet. 2011 May 13;88(5):523-35.

(42) Jablensky AV, Morgan V, Zubrick SR, Bower C, Yellachich LA. Pregnancy, delivery, and neonatal complications in a population cohort of women with schizophrenia and major affective disorders. Am J Psychiatry. 2005 Jan;162(1):79-91.

(43) Suvisaari JM, Taxell-Lassas V, Pankakoski M, Haukka JK, Lönnqvist JK, Häkkinen LT. Obstetric complications as risk factors for schizophrenia spectrum psychoses in offspring of mothers with psychotic disorder. Schizophr Bull. 2013 Sep;39(5):1056-66.

(44) Torniainen, M. Cognitive Impairment in Schizophrenia: Related Risk Factors and Clinical Characteristics (dissertation). Helsinki, Finland; National Institute for Health and Welfare (THL); 2013. 100 pages.

(45) Snell BJ. Assessment and management of bleeding in the first trimester of pregnancy. J Midwifery Womens Health. 2009 Nov-Dec;54(6):483-91.

(46) Laughon SK, Berghella V, Reddy UM, Sundaram R, Lu Z, Hoffman MK. Neonatal and maternal outcomes with prolonged second stage of labor. Obstet Gynecol. 2014 Jul;124(1):57-67. Erratum in: Obstet Gynecol. 2014 Oct;124(4):842.

(47) Olesen AW, Westergaard JG, Olsen J. Perinatal and maternal complications related to postterm delivery: a national register-based study, 1978-1993. Am J Obstet Gynecol. 2003 Jul;189(1):222-7.

(48) Caughey AB, Washington AE, Laros RK Jr. Neonatal complications of term pregnancy: rates by gestational age increase in a continuous, not threshold, fashion. Am J Obstet Gynecol. 2005 Jan;192(1):185-90.

(49) Galal M, Symonds I, Murray H, Petraglia F, Smith R. Postterm pregnancy. Facts Views Vis Obgyn. 2012;4(3):175-87.

(50) Taipale P, Hiilesmaa V. Predicting delivery date by ultrasound and last menstrual period in early gestation. Obstet Gynecol. 2001 Feb;97(2):189-94.

(51) Afolabi AF, Adeyemi, AS. Grand-multiparity: Is it still an obstetric risk? Open Journal of Obstetrics and Gynecology, 2013 Jun;3(4):411-415.

(52) Lahti M, Eriksson JG, Heinonen K, Kajantie E, Lahti J, Wahlbeck K, Tuovinen S, Pesonen AK, Mikkonen M, Osmond C, Räikkönen K. Maternal Grand Multiparity and the Risk of Severe Mental Disorders in Adult Offspring. PLoS One. 2014 Dec 10;9(12):e114679.

(53) Kemppainen L, Mäkikyrö T, Jokelainen J, Nieminen P, Järvelin MR, Isohanni M. Is grand multiparity associated with offsprings' hospital-treated mental disorders? A 28-year follow-up of the North Finland 1966 birth cohort. Soc Psychiatry Psychiatr Epidemiol. 2000 Mar;35(3):104-8.

(54) Jacquemyn Y, Vermeulen K, Vellinga S. A Systematic Review of Grand Multiparity. Current Women s Health Reviews. 2006 Feb:2(1):25-32.

(55) Babinszki A, Kerenyi T, Torok O, Grazi V, Lapinski RH, Berkowitz RL. Perinatal outcome in grand and great-grand multiparity: effects of parity on obstetric risk factors. Am J Obstet Gynecol. 1999 Sep;181(3):669-74.

(56) Baskett TF. Grand multiparity - a continuing threat: a 6-year review. Can Med Assoc J. 1977 May 7;116(9):1001-4.

(57) Bugg GJ, Atwal GS, Maresh M. Grandmultiparae in a modern setting. BJOG. 2002 Mar;109(3):249-53.

(58) Pallasmaa N, Gissler M. Synnytysten trendejä Suomessa. Suomen Lääkärilehti. 2016;71(25-32):1860-1866.

(59) Jolly MC, Sebire NJ, Harris JP, Regan L, Robinson S. Risk factors for macrosomia and its clinical consequences: a study of 350,311 pregnancies. Eur J Obstet Gynecol Reprod Biol. 2003 Nov 10;111(1):9-14.

(60) Purho J, Nuutila M, Heikinheimo O. Kaksosraskaudet. Duodecim. 2008;124(10):1111-9.

(61) Hänninen SL. Kätilötyön vaiheita. Helsinki: Otava; 1965. Chapter 5, p 228-229, 234-235, 237.

(62) Viisainen K. Choices in Birth Care - The Place of Birth. Helsinki: Gummerus Printing; 2000. Chapter 2, p 15-16.